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2nd M.S.O.BUILDING,
234/4,ACHARYA JAGADISH CHANDRA BOSE ROAD,
CALCUTTA-700 020

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(71) Applicant : M/s..ALEMBIC CHEMICAL WORKS COMPANY LIMITED, ALEMBIC ROAD, VADODARA 390 003, GUJARAT,

(72) Inventor:
(1) JOYENDU JAGADINDU CHAUDHURI

(74) Agent : M/S.RAMU & ASSOCIATES

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EXAMINER : DR.RUCHI TIWARI

(54) Title : A PROCESS OF PREPARING STABLE AZITHROMYCIN ORAL SUSPENSION LIQUID COMPOSITION.

(57) Abstract : The process of preparing a stable Azithromycin oral suspension liquid composition which ensures the stability of the active drug Azithromycin in ready to use liquid form . In addition this dosage form masks the characteristic unpleasant taste of the active drug by the use of suitable flavouring agents, thereby, enhancing the palatability of the drug in the ready to use liquid dosage form comprising the following steps:

a) taking desired quantity of purified water into a manufacturing tank and adding sucrose of 5% to 80% w/v, under continuous stirring and heating the content to completely dissolve the sucrose and further heating the syrup for 5 to 15 minutes.

b) dissolving Sodium Methyl Hydroxybenzoate (0.015 to 0.2% w/v) and sodium propyl Hydroxybenzoate (0.001 to 0.1% w/v) in hot purified water in separate vessel, passing the solution through (# 60 to 100) sieve and mixing the same into the syrup of step (a), and then filtering the hot syrup bulk, preferably through a filter press, using siliceous earth as filter acid, and cooling the same to ambient temperature,

c) transferring a desired quantity (20 to 40% of syrup bulk of step (b) into another vessel,

PRICE : THIRTY RUPEES

d) dissolving polysorbate 40,60 or 80 (0.005 to 5.0% w/v) into warm purified water in a separate container and sieving the same through (# 60 to 100) sieve and adding into the syrup of step c under stirring to mix well,

e) transferring Azithromycin Dihydrate (4 to 5% w/v) into the mix of step (d), under continuous stirring to obtain uniform homogenous slurry free from lumps,

f) adding colloidal silicon Dioxide (0.05 to 10% w/v) to the slurry of step (e), under continuous stirring to obtain homogenous dispersion and transferring the same into the syrup bulk of step (b) kept in the manufacturing tank,

g) dissolving sodium citrate (0.05 to 5% w/v) in warm purified water in a separate vessel, sieving the solution through # 60 to 160 sieve and mixing the same into the dispersing/slurry of step (f), kept in the manufacturing tank,

h) taking hot purified water into a container, adding sodium carboxy methyl cellulose (0.1 to 0.2% w/v) under continuous stirring to form uniform slurry, sieving through # 40 sieve and mixing the same into the slurry of step (g) kept in the manufacturing tank,

i) dissolving Monoammonium Glycyrrhizinate (0.001 to 5% w/v) in warm purified water, in a separate container, under continuous stirring, filtering the solution through # 60 to 100 sieve and mixing the same into the slurry of step (h), kept into the manufacturing tank,

j) dissolving Tartrazine (0.001 to 1% w/v) in warm purified water, under continuous stirring, sieving through # 60 to 100 sieve and mixing into the slurry to step (I), kept in the manufacturing tank,

k) checking and adjusting pH, if necessary with 10% w/v sodium Hydroxide solution to maintain pH in between 7 to 9, preferably from 7.5 to 8.5,

l) homogenising the bulk preferably by passing though the colloidal mill and deaerating the product by using vacuum,

m) dissolving propylene Glycol (up to 5% w/v), Menthol (up to 5% w/v), and adding pepper mint flavour preferably C-7531 (BBA) from 0.05 to 5% w/v, in a separate vessel stirring and sieving the solution through # 60 to 100 sieve and mixing the clear solution into the bulk of step (l) kept in the manufacturing tank,

n) making up the desired volume buy mixing purified water to obtain Azithromycin oral suspension liquid composition.

FORM - 2

THE PATENTS ACT, 1970

COMPLETE
SPECIFICATION

SECTION 10

TITLE : **A PROCESS OF PREPARING STABLE AZITHROMYCIN ORAL SUSPENSION LIQUID COMPOSITION**

APPLICANT : **M/s..ALEMBIC CHEMICAL WORKS COMPANY LIMITED, ALEMBIC ROAD, VADODARA 390 003, GUJARAT. AN INDIAN COMPANY INCORPORATED UNDER THE COMPANIES ACT,1956.**

The following Specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed : -

This invention relates to a process of preparing a stable Azithromycin oral suspension liquid composition.

More particularly this invention relates to a process of preparing a stable Azithromycin suspension liquid composition which is more stable than the existing conventional liquid dosage form of Azithromycin, uniform suspension with a very negligible batch to batch variation, having good taste, high viscosity and preservation efficacy.

According to this invention the process of preparing a stable Azithromycin oral suspension liquid composition which ensures the stability of the active drug Azithromycin in ready to use liquid dosage form. In addition this dosage form masks the characteristic unpleasant taste of the active drug by the use of suitable flavouring agents, thereby, enhancing the platability of the drug in the ready to use liquid dosage form comprising the following steps:

a) taking desired quantity of purified water into a manufacturing tank and adding sucrose of about 5 to 80%w/v, under continuous stirring and heating the content to completely dissolve the sucrose and further heating the syrup for 5 to 15 minutes.

b) Dissolving Sodium Methyl Hydroybenzoate (0.015 to 0.2%w/v) and sodium propyl Hydroxybenzoate (0.001 to 0.1%w/v) in hot purified water in separate vessel, passing the solution through (# 60 to 100) sieve and mixing the same into the syrup of step (a), and then filtering the hot syrup bulk, preferably through a filter press, using siliceous earth as filter acid, and cooling the same to ambient temperature,

c) Transferring a desired quantity (20 to 40% of syrup bulk of step (b) into another vessel,

d) Dissolving polysorbate 40,60 or 80 (0.005 to 5.0%w/v) into warm purified water in a separate container and seiving the same through (# 60 to 100) sieve and adding into the syrup of step (c) under stirring to mix well,

e) Transferring Azithromycin Dihydrate (4 to 5%w/v) into the mix of step (d), under continuous stirring to obtain uniform homogenous slurry free from lumps,

f) Adding colloidal silicon Dioxide (0.05 to 10%w/v) to the slurry of step (e), under continuous stirring to obtain homogenous dispersion and transferring the same into the syrup bulk of step (b) kept in the manufacturing tank,

g) Dissolving sodium citrate (0.05 to 5%w/v) in warm purified water in a separate vessel, sieving the solution through # 60 to 160 sieve and mixing the same into the dispersing/slurry of step (f), kept in the manufacturing tank,

h) Taking hot purified water into a container, adding sodium carboxy methyl cellulose (0.1 to 0.2%w/v) under continuous stirring to form uniform slurry, sieving through # 40 sieve and mixing the same into the slurry of step (g) kept in the manufacturing tank,

i) Dissolving Monoammonium Glycyrrhizinate (0.001 to 5%w/v) in warm purified water, in a separate container, under continuous stirring, filtering the solution through # 60 to 100 sieve and mixing the same into the slurry of step (h), kept into the manufacturing tank,

j) Dissolving Tartrazine (0.001 to 1%w/v) in warm purified water, under continuous stirring, sieving through # 60 to 100 sieve and mixing into the slurry to step (I), kept in the manufacturing tank,

k) Checking and adjusting pH, if necessary with 10% w/v sodium Hydroxide solution to maintain pH in between 7 to 9, preferably from 7.5 to 8.5,

l) Homogenising the bulk preferably by passing though the colloidal mill and deaerating the product by using vacuum,

m) Dissolving propylene Glycol (up to 5% w/v), Menthol (up to 5% w/v), and adding pepper mint flavour preferably C-7531 (BBA) from 0.05 to 5% w/v, in a separate vessel stirring and sieving the solution through # 60 to 100 sieve and mixing the clear solution into the bulk of step (1) kept in the manufacturing tank,

n) Making up the desired volume by mixing purified water to obtain Azithromycin oral suspension liquid composition.

In the above process the polysorbate used in step (d) is polysorbate 60.

In the above process the said colloidal silicon Dioxide used in step (f), is colloidal silicon Dioxide (5M).

In the above process, the sieving in steps (b), (d), (g), (I), (j), & (m), is carried out by using # 80 S.S. sieve.

In the above process the said liquid composition after approval is filled in suitable containers preferably amber glass bottles under continuous moderate stirring and sealed, preferably with pilfer proof aluminium cap with E.P. Wad.

In the above process, the said manufacturing tank is a steam jacketed stainless steel (S.S.) manufacturing tank.

In the above process, the said other vessels and/or containers used are made of stainless steel.

In the above process, the said vessels and/or containers are rinsed with purified water and rinsing is added and mixed to the bulk in the manufacturing tank.

The invention will be clear with the help of the following examples:-

Example - 1

Batch size : 1000 ml

Sr. No.	Ingredients	Quantity in g.
1	Azithromycin Dihydrate	42.000 g
2	Sucrose	700.0 g
3	Sodium methyl Hydroxybenzoate	0.500 g
4	Sodium Propyl Hydroxybenzoate	0.200 g
5	Sodium Carboxy Methyl Cellulose	0.500 g
6	Polysorbate 60	0.100 g
7	Colloidal Silicon Dioxide (5M)	1.000 g
8	Monoammonium Glycyrrhizinate	5.000 g
9	Sodium Citrate	0.500 g
10	Menthol	0.010 g
11	Tartrazine	0.100 g
12	Propylene Glycol	1.000 g
13	Peppermint Flavour	2.000 ml
14	Purified Water	q.s.

Manufacturing Process:

1. Transfer Purified Water to a suitable jacketed s.s. manufacturing tank. Add Sucrose with continuous stirring and heat the content with stirring till sucrose is completely dissolved. Boil the syrup for 10 minutes.

Sucrose : 700.0 g

Purified Water : 350.0 ml

2. Dissolve Sodium Methyl Hydroxybenzoate and Sodium Propyl Hydroxybenzoate in hot purified water in a suitable s.s. vessel. Transfer the solution to the main manufacturing tank while passing it through # 80 s.s. sieve and stir to mix. Rinse the container with purified water and the rinsings to the bulk. Stir to mix.

   Sodium Methyl Hydroxybenzoate : 0.500 g

   Sodium propyl Hydroxybenzoate : 0.200 g

   Purified Water : 5.0 ml

3. Filter the hot syrup bulk through "Filter Press" using Purified Siliceous Earth as filter aid. Cool the syrup to ambient temperature.

4. Transfer a portion of the above syrup bulk (about 300.000 ml) to another suitable s.s. vessel.

5. Transfer Polysorbate 60 to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the syrup (step 4) while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

   Polysorbate 60 : 0.100 g

   Purified Water : 10.00 ml

6. Transfer Azithromycin Dihydrate to the s.s. vessel (step 4) with continuous stirring. Stir to obtain a uniform homogenous slurry free from lumps.

   Azithromycin Dihydrate : 42.000 g

7. Transfer Colloidal Silicon Dioxide to the s.s. vessel (step 4) with continuous stirring. Stir well to achieve homogenous dispersion. Transfer the resulting uniform slurry to the main manufacturing tank with continuous stirring. Stir to mix.

   Colloidal Silicon Dioxide (5M) : 1.000 g

8. Transfer Sodium Citrate to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

Sodium Citrate : 0.500 g

Purified Water : 15.0 ml

9. Transfer hot Purified Water to a suitable s.s. container. Add sodium Carboxy Methyl Cellulose with continuous stirring. Continue stirring till uniform slurry is obtained. Transfer the uniform slurry to the manufacturing tank while filtering through # 40 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

   Sodium Carboxy Methyl Cellulose : 0.500 g

   Purified Water : 20.0 ml

10. Transfer Monoammonium Glyrrhizinate to a suitble s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank. Stir to mix.

    Monoammonium Glycyrrhizinate : 5.000 g

    Purified Water : 40.0 ml

11. Transfer Tartrazine to a suitable s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

    Tartrazine : 0.100 g

    Purified Water : 5.0 ml

12. Check and adjust the pH 8.4, if necessary with 10% w/v Sodium Hydroxide solution.

13. Homogenise the bulk by passing through the colloidal millwith suitable clearance and deaerate the product using vacuum.

14. Add Propylene Glycol to a suitable s.s. container, add Menthol and stir to dissolve. Add Peppermint Flavour C-7531 (BBA) and stir to mix. Transfer the clear solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

Propylene Glycol : 1.000 g

Menthol : 0.010 g

Peppermint Flavour : 2.00 ml

15. Make up the volume to 1000 ml with Purified Water and mix.

16. Send the sample for analysis of pH determination and Assay of Azithromycin.

17. After getting approval fill the product in amber glass bottle under continuous moderate stirring and seal the bottle with pilfer proof aluminium cap with E.P. wad.

Example : 2

Batch size : 1000 ml

Sr. No.	Ingredients	Quantity in g.
1	Azithromycin Dihydrate	42.000 g
2	Sucrose	770.0 g
3	Sodium Methyl Hydroxybenzoate	2.000 g
4	Sodium Propyl Hydroxybenzoate	1.000 g
5	Sodium Carboxy Methyl Cellulose	1.500 g
6	Polysorbate 60	2.000 g
7	Colloidal Silicon Dioxide (5M)	5.000 g
8	Monoammonium Glycyrrhizinate	10.000 g
9	Sodium Citrate	13.000 g
10	Menthol	0.080 g
11	Tartrazine	1.000 g
12	Propylene Glycol	10.000 g
13	Peppermint Flavour	5.000 ml
14	Purified Water	q.s.

Manufacturing Process:

1. Transfer Purified Water to a suitable jacketed s.s. manufacturing tank. Add Sucrose with continuous stirring and heat the content with stirring till sucrose is completely dissolved. Boil the syrup for 10 minutes.

   Sucrose : 770.0 g

   Purified Water : 385.0 ml

2. Dissolve Sodium Methyl Hydroxybenzoate and Sodium Propylhydroxybenzoate in hot purified water in a suitable s.s. vessel. Transfer the solution to the main manufacturing tank while passing it through # 80 s.s. sieve and stir to mix. Rinse the container with purified water and the rinsings to the bulk. Stir to mix.

   Sodium Methyl Hydroxybenzoate : 2.000 g

   Sodium propyl Hydroxybenzoate : 1.000 g

   Purified Water : 10.0 ml

3. Filter the hot syrup bulk through "Filter Press" using Purified Siliceous Earth as filter aid. Cool the syrup to ambient temperature.

4. Transfer a portion of the above syrup bulk (about 300.000 ml) to another suitable s.s. vessel.

5. Transfer Polysorbate 60 to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the syrup (step 4) while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

   Polysorbate 60 : 2.000 g

   Purified Water : 20.00 ml

6. Transfer Azithromycin Dihydrate to the s.s. vessel (step 4) with continuous stirring. Stir to obtain a uniform homogenous slurry free from lumps.

   Azithromycin Dihydrate : 42.000 g

7. Transfer Colloidal Silicon Dioxide to the s.s. vessel (step 4) with continuous stirring. Stir well to achieve homogenous dispersion. Transfer the resulting uniform slurry to the main manufacturing tank with continuous stirring. Stir to mix.

   Colloidal Silicon Dioxide (5M) : 5.000 g

8. Transfer Sodium Citrate to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

Sodium Citrate	:	13.000 g
Purified Water	:	260.0 ml

9. Transfer hot Purified Water to a suitable s.s. container. Add sodium Carboxy Methyl Cellulose with continuous stirring. Continue stirring till uniform slurry is obtained. Transfer the uniform slurry to the manufacturing tank while filtering through # 40 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

Sodium Carboxy Methyl Cellulose	:	1.500 g
Purified Water	:	60.00 ml

10. Transfer Monoammonium Glyrrhizinate to a suitble s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank. Stir to mix.

Monoammonium Glycyrrhizinate	:	10.000 g
Purified Water	:	80.0 ml

11. Transfer Tartrazine to a suitable s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

Tartrazine	:	1.000 g
Purified Water	:	10.0 ml

12. Check and adjust the pH 8.4, if necessary with 10% w/v Sodium Hydroxide solution.

13. Homogenise the bulk by passing through the colloidal mill with suitable clearance and deaerate the product using vacuum.

14. Add Propylene Glycol to a suitable s.s. container, add Menthol and stir to dissolve.

Add Peppermint Flavour C-7531 (BBA) and stir to mix. Transfer the clear solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

Propylene Glycol	:	10.000 g
Menthol	:	0.080 g
Peppermint Flavour	:	5.00 ml

15. Make up the volume to 1000 ml with Purified Water and mix.

16. Send the sample for analysis of pH determination and Assay of Azithromycin.

17. After getting approval fill the product in amber glass bottle under continuous moderate stirring and seal the bottle with pilfer proof aluminium cap with E.P. wad.

Example - 3

Batch size : 1000 ml

Sr. No.	Ingredients	Quantity in g.
1	Azithromycin Dihydrate	42.000 g
2	Sucrose	500.0 g
3	Sodium Methyl Hydroxybenzoate	1.000 g
4	Sodium Propyl Hydroxybenzoate	0.100 g
5	Sodium Carboxy Methyl Cellulose	3.000 g
6	Polysorbate 60	0.200 g
7	Colloidal Silicon Dioxide (5M)	1.000 g
8	Monoammonium Glycyrrhizinate	1.500 g
9	Sodium Citrate	2.000 g
10	Menthol	0.010 g
11	Tartrazine	0.050 g

12	Propylene Glycol	1.000 g
13	Peppermint Flavour	2.000 ml
14	Purified Water	q.s.

Manufacturing Process:

1. Transfer Purified Water to a suitable jacketed s.s. manufacturing tank. Add Sucrose with continuous stirring and heat the content with stirring till sucrose is completely dissolved. Boil the syrup for 10 minutes.

   Sucrose : 500.0 g

   Purified Water : 350.0 ml

2. Dissolve Sodium Methyl Hydroxybenzoate and Sodium Propylhydroxybenzoate in hot purified water in a suitable s.s. vessel. Transfer the solution to the main manufacturing tank while passing it through # 80 s.s. sieve and stir to mix. Rinse the container with purified water and the rinsings to the bulk. Stir to mix.

   Sodium Methyl Hydroxybenzoate : 1.000 g

   Sodium propyl Hydroxybenzoate : 0.100 g

   Purified Water : 5.0 ml

3. Filter the hot syrup bulk through "Filter Press" using Purified Siliceous Earth as filter aid. Cool the syrup to ambient temperature.

4. Transfer a portion of the above syrup bulk (about 300.000 ml) to another suitable s.s. vessel.

5. Transfer Polysorbate 60 to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the syrup (step 4) while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

   Polysorbate 60 : 0.200 g

   Purified Water : 10.00 ml

6. Transfer Azithromycin Dihydrate to the s.s. vessel (step 4) with continuous stirring. Stir to obtain a uniform homogenous slurry free from lumps.

Azithromycin Dihydrate : 42.000 g

7. Transfer Colloidal Silicon Dioxide to the s.s. vessel (step 4) with continuous stirring. Stir well to achieve homogenous dispersion. Transfer the resulting uniform slurry to the main manufacturing tank with continuous stirring. Stir to mix.

   Colloidal Silicon Dioxide (5M) : 1.000 g

8. Transfer Sodium Citrate to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

   Sodium Citrate : 2.000 g

   Purified Water : 15.0 ml

9. Transfer hot Purified Water to a suitable s.s. container. Add sodium Carboxy Methyl Cellulose with continuous stirring. Continue stirring till uniform slurry is obtained. Transfer the uniform slurry to the manufacturing tank while filtering through # 40 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

   Sodium Carboxy Methyl Cellulose : 3.000 g

   Purified Water : 20.0 ml

10. Transfer Monoammonium Glyrrhizinate to a suitble s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank. Stir to mix.

    Monoammonium Glycyrrhizinate : 1.500 g

    Purified Water : 40.0 ml

11. Transfer Tartrazine to a suitable s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

    Tartrazine : 0.050 g

    Purified Water : 5.0 ml

12. Check and adjust the pH 8.4, if necessary with 10% w/v Sodium Hydroxide solution.

13. Homogenise the bulk by passing through the colloidal mill with suitable clearance and deaerate the product using vacuum.

14. Transfer Peppermint Flavour C-7531 (BBA) and stir to mix. Transfer the clear solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

    Peppermint Flavour : 2.00 ml

15. Make up the volume to 1000 ml with Purified Water and mix.

16. Send the sample for analysis of pH determination and Assay of Azithromycin.

17. After getting approval fill the product in amber glass bottle under continuous moderate stirring and seal the bottle with pilfer proof aluminium cap with E.P. wad.

Example - 4

Batch size : 1000 ml

Sr. No.	Ingredients	Quantity in g.
1	Azithromycin Dihydrate	42.000 g
2	Sucrose	400.0 g
3	Sodium Methyl Hydroxybenzoate	1.200 g
4	Sodium Propyl Hydroxybenzoate	0.120 g
5	Sodium Carboxy Methyl Cellulose	5.000 g
6	Polysorbate 60	0.500 g
7	Colloidal Silicon Dioxide (5M)	0.500 g
8	Monoammonium Glycyrrhizinate	2.000 g
9	Sodium Citrate	5.000 g
10	Menthol	0.500 g
11	Tartrazine	0.400 g

12	Propylene Glycol	5.000 g
13	Peppermint Flavour	5.000 ml
14	Purified Water	q.s.

Manufacturing Process:

1. Transfer Purified Water to a suitable jacketed s.s. manufacturing tank. Add Sucrose with continuous stirring and heat the content with stirring till sucrose is completely dissolved. Boil the syrup for 10 minutes.

   Sucrose : 400.0 g

   Purified Water : 200.0 ml

2. Dissolve Sodium Methyl Hydroxybenzoate and Sodium Propylhydroxybenzoate in hot purified water in a suitable s.s. vessel. Transfer the solution to the main manufacturing tank while passing it through # 80 s.s. sieve and stir to mix. Rinse the container with purified water and the rinsings to the bulk. Stir to mix.

   Sodium Methyl Hydroxybenzoate : 1.200 g

   Sodium propyl Hydroxybenzoate : 0.120 g

   Purified Water : 10.0 ml

3. Filter the hot syrup bulk through "Filter Press" using Purified Siliceous Earth as filter aid. Cool the syrup to ambient temperature.

4. Transfer a portion of the above syrup bulk (about 300.000 ml) to another suitable s.s. vessel.

5. Transfer Polysorbate 60 to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the syrup (step 4) while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

   Polysorbate 60 : 0.500 g

   Purified Water : 25.00 ml

6. Transfer Azithromycin Dihydrate to the s.s. vessel (step 4) with continuous stirring. Stir to obtain a uniform homogenous slurry free from lumps.

Azithromycin Dihydrate : 42.000 g

7. Transfer Colloidal Silicon Dioxide to the s.s. vessel (step 4) with continuous stirring. Stir well to achieve homogenous dispersion. Transfer the resulting uniform slurry to the main manufacturing tank with continuous stirring. Stir to mix.

   Colloidal Silicon Dioxide (5M) : 0.500 g

8. Transfer Sodium Citrate to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

   Sodium Citrate : 5.000 g

   Purified Water : 110.0 ml

9. Transfer hot Purified Water to a suitable s.s. container. Add sodium Carboxy Methyl Cellulose with continuous stirring. Continue stirring till uniform slurry is obtained. Transfer the uniform slurry to the manufacturing tank while filtering through # 40 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

   Sodium Carboxy Methyl Cellulose : 5.000 g

   Purified Water : 150.0 ml

10. Transfer Monoammonium Glyrrhizinate to a suitble s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank. Stir to mix.

    Monoammonium Glycyrrhizinate : 2.000 g

    Purified Water : 15.0 ml

11. Transfer Tartrazine to a suitable s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

    Tartrazine : 0.400 g

    Purified Water : 5.0 ml

12. Check and adjust the pH 8.4, if necessary with 10% w/v Sodium Hydroxide solution.

13. Homogenise the bulk by passing through the colloidal mill with suitable clearance and deaerate the product using vacuum.

14. Add Propylene Glycol to a suitable s.s. container, add menthol and stir to dissolve. Add Peppermint Flavour C-7531 (BBA) and stir to mix. Transfer the clear solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

Propylene Glycol	:	5.000 g
Menthol	:	0.500 g
Peppermint Flavour	:	5.00 ml

15. Make up the volume to 1000 ml with Purified Water and mix.

16. Send the sample for analysis of pH determination and Assay of Azithromycin.

17. After getting analytical approval fill the product in amber glass bottle under continuous moderate stirring and seal the bottle with pilfer proof aluminium cap with E.P. wad.

Summary of results for experimental lots

Sr. No.	Parameters	Initial	Results After 6 months stability at 40+-2*C/75%+-5% RH
1.	Appearance	++++	+++
2.	Colour	++++	+++
3.	Flavour	++++	+++
4.	PH*	8.5	8.0
5.	Viscosity	+++	++
6.	Redispersibility	+++	++
7.	Palatability	++++	+++

8.	Pourability	+++	++
9.	Dissolution *	93.20	91.80
10.	Assay *	99.48	98.30

Not Good - +

Satisfactory - ++

Good - +++

Very Good - ++++

*Limits:

1. pH : 7.0 - 9.0
2. Dissolution : Not less than 80.0% of the label claim is dissolved in 45 minutes.
3. Assay : Not less than 90.0% and not more than 110.0% of the label claim.

Example - 5

Batch size : 1000 ml

Sr. No.	Ingredients	Quantity in g.
1	Azithromycin Dihydrate	42.000 g
2	Sucrose	100.0 g
3	Sodium Methyl Hydroxybenzoate	1.200 g
4	Sodium Propyl Hydroxybenzoate	0.120 g
5	Sodium Carboxy Methyl Cellulose	1.000 g
6	Polysorbate 60	10.000 g
7	Colloidal Silicon Dioxide (5M)	20.000 g
8	Monoammonium Glycyrrhizinate	20.000 g

9	Sodium Citrate	10.000 g
10	Menthol	
11	Tartrazine	1.000 g
12	Propylene Glycol	
13	Peppermint Flavour	4.000 ml
14	Purified Water	q.s.

Manufacturing Process:

1. Transfer Purified Water to a suitable jacketed s.s. manufacturing tank. Add Sucrose with continuous stirring and heat the content with stirring till sucrose is completely dissolved. Boil the syrup for 10 minutes.

   Sucrose : 100.0 g

   Purified Water : 50.0 ml

2. Dissolve Sodium Methyl Hydroxybenzoate and Sodium Propylhydroxybenzoate in hot purified water in a suitable s.s. vessel. Transfer the solution to the main manufacturing tank while passing it through # 80 s.s. sieve and stir to mix. Rinse the container with purified water and the rinsings to the bulk. Stir to mix.

   Sodium Methyl Hydroxybenzoate : 1.200 g

   Sodium propyl Hydroxybenzoate : 0.120 g

   Purified Water : 12.0 ml

3. Filter the hot syrup bulk through "Filter Press" using Purified Siliceous Earth as filter aid. Cool the syrup to ambient temperature.

4. Transfer a portion of the above syrup bulk (about 300.000 ml) to another suitable s.s. vessel.

5. Transfer Polysorbate 60 to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the syrup (step 4) while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

Polysorbate 60 : 10.000 g

Purified Water : 80.00 ml

6. Transfer Azithromycin Dihydrate to the s.s. vessel (step 4) with continuous stirring. Stir to obtain a uniform homogenous slurry free from lumps.

   Azithromycin Dihydrate : 42.000 g

7. Transfer Colloidal Silicon Dioxide to the s.s. vessel (step 4) with continuous stirring. Stir well to achieve homogenous dispersion. Transfer the resulting uniform slurry to the main manufacturing tank with continuous stirring. Stir to mix.

   Colloidal Silicon Dioxide (5M) : 20.000 g

8. Transfer Sodium Citrate to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

   Sodium Citrate : 10.000 g

   Purified Water : 220.0 ml

9. Transfer hot Purified Water to a suitable s.s. container. Add sodium Carboxy Methyl Cellulose with continuous stirring. Continue stirring till uniform slurry is obtained. Transfer the uniform slurry to the manufacturing tank while filtering through # 40 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

   Sodium Carboxy Methyl Cellulose : 1.000 g

   Purified Water : 40.0 ml

10. Transfer Monoammonium Glyrrhizinate to a suitble s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank. Stir to mix.

Monoammonium Glycyrrhizinate : 20.000 g

Purified Water : 200.0 ml

11. Transfer Tartrazine to a suitable s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

    Tartrazine : 1.000 g

    Purified Water : 10.0 ml

12. Check and adjust the pH 8.4, if necessary with 10% w/v Sodium Hydroxide solution.

13. Homogenise the bulk by passing through the colloidal mill with suitable clearance and deaerate the product using vacuum.

14. Transfer Peppermint Flavour C-7531 (BBA) and stir to mix. Transfer the clear solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

    Peppermint Flavour : 4.00 ml

15. Make up the volume to 1000 ml with Purified Water and mix.

16. Send the sample for analysis of pH determination and Assay of Azithromycin.

17. After getting analytical approval fill the product in amber glass bottle under continuous moderate stirring and seal the bottle with pilfer proof aluminium cap with E.P. wad.

Summary of results for experimental lots

Sr. No.	Parameters	Initial	Results After 6 months stability at 40+-2*C/75%+-5% RH
1.	Appearance	+++	++
2.	Colour	+++	++
3.	Flavour	++	++

4.	PH*	8.5	8.0
5.	Viscosity	+++	++
6.	Redispersibility	+++	++
7.	Palatability	+++	++
8.	Pourability	+++	++
9.	Dissolution *	89.60	85.20
10.	Assay *	100.26	98.25

Not Good - +

Satisfactory - ++

Good - +++

Very Good - ++++

* Limits:

1. pH : 7.0 - 9.0
2. Dissolution : Not less than 80.0% of the label claim is dissolved in 45 minutes.
3. Assay : Not less than 90.0% and not more than 110.0% of the label claim.

Example - 6

Batch size : 1000 ml

Sr. No.	Ingredients	Quantity in g.
1	Azithromycin Dihydrate	42.000 g
2	Sucrose	50.00 g
3	Sodium Methyl Hydroxybenzoate	1.000 g
4	Sodium Propyl Hydroxybenzoate	0.100 g

5	Sodium Carboxy Methyl Cellulose	8.000 g
6	Polysorbate 60	13.000 g
7	Colloidal Silicon Dioxide (5M)	50.000 g
8	Monoammonium Glycyrrhizinate	30.000 g
9	Sodium Citrate	10.000 g
10	Menthol	
11	Tartrazine	1.500 g
12	Propylene Glycol	
13	Peppermint Flavour	6.000 ml
14	Purified Water	q.s.

Manufacturing Process:

1. Transfer Purified Water to a suitable jacketed s.s. manufacturing tank. Add Sucrose with continuous stirring and heat the content with stirring till sucrose is completely dissolved. Boil the syrup for 10 minutes.

   Sucrose : 50.0 g

   Purified Water : 25.0 ml

2. Dissolve Sodium Methyl Hydroxybenzoate and Sodium Propylhydroxybenzoate in hot purified water in a suitable s.s. vessel. Transfer the solution to the main manufacturing tank while passing it through # 80 s.s. sieve and stir to mix. Rinse the container with purified water and the rinsings to the bulk. Stir to mix.

   Sodium Methyl Hydroxybenzoate : 1.000 g

   Sodium propyl Hydroxybenzoate : 0.100 g

   Purified Water : 10.0 ml

3. Filter the hot syrup bulk through "Filter Press" using Purified Siliceous Earth as filter aid. Cool the syrup to ambient temperature.

4. Transfer a portion of the above syrup bulk (about 300.000 ml) to another suitable s.s. vessel.

5. Transfer Polysorbate 60 to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the syrup (step 4) while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

   Polysorbate 60 : 13.000 g

   Purified Water : 100.00 ml

6. Transfer Azithromycin Dihydrate to the s.s. vessel (step 4) with continuous stirring. Stir to obtain a uniform homogenous slurry free from lumps.

   Azithromycin Dihydrate : 42.000 g

7. Transfer Colloidal Silicon Dioxide to the s.s. vessel (step 4) with continuous stirring. Stir well to achieve homogenous dispersion. Transfer the resulting uniform slurry to the main manufacturing tank with continuous stirring. Stir to mix.

   Colloidal Silicon Dioxide (5M) : 50.000 g

8. Transfer Sodium Citrate to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

   Sodium Citrate : 10.000 g

   Purified Water : 220.0 ml

9. Transfer hot Purified Water to a suitable s.s. container. Add sodium Carboxy Methyl Cellulose with continuous stirring. Continue stirring till uniform slurry is obtained. Transfer the uniform slurry to the manufacturing tank while filtering through # 40 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

   Sodium Carboxy Methyl Cellulose : 8.000 g

Purified Water : 250.0 ml

10. Transfer Monoammonium Glyrrhizinate to a suitble s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank. Stir to mix.

    Monoammonium Glycyrrhizinate : 30.000 g

    Purified Water : 300.0 ml

11. Transfer Tartrazine to a suitable s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

    Tartrazine : 1.500 g

    Purified Water : 15.0 ml

12. Check and adjust the pH 8.4, if necessary with 10% w/v Sodium Hydroxide solution.

13. Homogenise the bulk by passing through the colloidal mill with suitable clearance and deaerate the product using vacuum.

14. Transfer Peppermint Flavour C-7531 (BBA) and stir to mix. Transfer the clear solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

    Peppermint Flavour : 6.00 ml

15. Make up the volume to 1000 ml with Purified Water and mix.

16. Send the sample for analysis of pH determination and Assay of Azithromycin.

17. After getting analytical approval fill the product in amber glass bottle under continuous moderate stirring and seal the bottle with pilfer proof aluminium cap with E.P. wad.

Summary of results for experimental lots

Sr. No.	Parameters	Initial	Results After 6 months stability at 40+-2*C/75%+-5% RH
1.	Appearance	+++	+++
2.	Colour	+++	+++
3.	Flavour	+++	++
4.	PH*	8.6	8.0
5.	Viscosity	+++	+++
6.	Redispersibility	+++	++
7.	Palatability	+++	++
8.	Pourability	+++	+++
9.	Dissolution *	92.30	89.50
10.	Assay *	100.10	97.30

Not Good - +

Satisfactory - ++

Good - +++

Very Good - ++++

* Limits:

1. pH : 7.0 - 9.0
2. Dissolution : Not less than 80.0% of the label claim is dissolved in 45 minutes.
3. Assay : Not less than 90.0% and nbot more than 110% of the label claim.

Example - 7

Batch size : 1000 ml

Sr. No.	Ingredients	Quantity in g.
1	Azithromycin Dihydrate	42.000 g
2	Sucrose	720.00 g
3	Sodium Methyl Hydroxybenzoate	2.000 g
4	Sodium Propyl Hydroxybenzoate	0.500 g
5	Sodium Carboxy Methyl Cellulose	0.100 g
6	Polysorbate 60	4.000 g
7	Colloidal Silicon Dioxide (5M)	8.000 g
8	Monoammonium Glycyrrhizinate	0.500 g
9	Sodium Citrate	2.000 g
10	Menthol	1.000 g
11	Tartrazine	2.000 g
12	Propylene Glycol	10.000 g
13	Peppermint Flavour	10.000 ml
14	Purified Water	q.s.

Manufacturing Process:

1. Transfer Purified Water to a suitable jacketed s.s. manufacturing tank. Add Sucrose with continuous stirring and heat the content with stirring till sucrose is completely dissolved. Boil the syrup for 10 minutes.

   Sucrose : 720.0 g

   Purified Water : 360.0 ml

2. Dissolve Sodium Methyl Hydroxybenzoate and Sodium Propylhydroxybenzoate in hot purified water in a suitable s.s. vessel. Transfer the solution to the main manufacturing tank while passing it through # 80 s.s. sieve and stir to mix. Rinse the container with purified water and the rinsings to the bulk. Stir to mix.

Sodium Methyl Hydroxybenzoate	:	2.000 g
Sodium propyl Hydroxybenzoate	:	0.500 g
Purified Water	:	20.0 ml

3. Filter the hot syrup bulk through "Filter Press" using Purified Siliceous Earth as filter aid. Cool the syrup to ambient temperature.

4. Transfer a portion of the above syrup bulk (about 300.000 ml) to another suitable s.s. vessel.

5. Transfer Polysorbate 60 to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the syrup (step 4) while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

Polysorbate 60	:	4.000 g
Purified Water	:	50.00 ml

6. Transfer Azithromycin Dihydrate to the s.s. vessel (step 4) with continuous stirring. Stir to obtain a uniform homogenous slurry free from lumps.

Azithromycin Dihydrate	:	42.000 g

7. Transfer Colloidal Silicon Dioxide to the s.s. vessel (step 4) with continuous stirring. Stir well to achieve homogenous dispersion. Transfer the resulting uniform slurry to the main manufacturing tank with continuous stirring. Stir to mix.

Colloidal Silicon Dioxide (5M)	:	8.000 g

8. Transfer Sodium Citrate to a suitable s.s. container. Add warm Purified Water and stir to dissolve. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add it to the s.s. vessel. Stir to mix well.

Sodium Citrate	:	2.000 g

Purified Water : 50.0 ml

9. Transfer hot Purified Water to a suitable s.s. container. Add sodium Carboxy Methyl Cellulose with continuous stirring. Continue stirring till uniform slurry is obtained. Transfer the uniform slurry to the manufacturing tank while filtering through # 40 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

   Sodium Carboxy Methyl Cellulose : 0.100 g

   Purified Water : 20.0 ml

10. Transfer Monoammonium Glyrrhizinate to a suitble s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank. Stir to mix.

    Monoammonium Glycyrrhizinate : 0.500 g

    Purified Water : 10.0 ml

11. Transfer Tartrazine to a suitable s.s. container. Add warm Purified Water and stir continuously till it is dissolved. Transfer the solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

    Tartrazine : 2.000 g

    Purified Water : 20.0 ml

12. Check and adjust the pH 8.4, if necessary with 10% w/v Sodium Hydroxide solution.

13. Homogenise the bulk by passing through the colloidal mill with suitable clearance and deaerate the product using vacuum.

14. Add Propylene Glycol to a suitable s.s. container, add menthol and stir to dissolve. Add Peppermint Flavour C-7531 (BBA) and stir to mix. Transfer the clear solution to the manufacturing tank while filtering through # 80 s.s. sieve and mix. Rinse the container with sufficient quantity of Purified Water and add to the manufacturing tank.

    Propylene Glycol : 10.000 g

    Menthol : 1.000 g

    Peppermint Flavour : 10.00 ml

15. Make up the volume to 1000 ml with Purified Water and mix.

16. Send the sample for analysis of pH determination and Assay of Azithromycin.

17. After getting analytical approval fill the product in amber glass bottle under continuous moderate stirring and seal the bottle with pilfer proof aluminium cap with E.P. wad.

Summary of results for experimental lots

Sr. No.	Parameters	Results	
		Initial	After 6 months stability at 40+-2*C/75%+-5% RH
1.	Appearance	+++	+++
2.	Colour	+++	++
3.	Flavour	+++	+++
4.	PH*	8.6	8.0
5.	Viscosity	++	++
6.	Redispersibility	+++	++
7.	Palatability	+++	++
8.	Pourability	+++	++
9.	Dissolution *	92.40	88.60
10.	Assay *	99.98	95.40

Not Good - +

Satisfactory - ++

Good - +++

Very Good - ++++

* Limits:

1. pH : 7.0 - 9.0

2. Dissolution : Not less than 80.0% of the label claim is dissolved in 45 minutes.

3. Assay : Not less than 90.0% and not more than 110% of the label claim.

The above description and examples is given to understand the invention rather than to limit its scope.

We claim:

1. A process of preparing stable Azithromycin oral suspension liquid composition which ensures the stability of the active drug Azithromycin in ready to use liquid form. In addition this dosage form masks the characteristic unpleasant taste of the active drug by the use of suitable flavouring agents, thereby, enhancing the palatability of the drug in the ready to use liquid dosage form comprising the following steps:

a) taking desired quantity of purified water into a manufacturing tank and adding sucrose of 5% to 80%w/v, under continuous stirring and heating the content to completely dissolve the sucrose and further heating the syrup for 5 to 15 minutes.

b) dissolving Sodium Methyl Hydroxybenzoate (0.015 to 0.2%w/v) and sodium propyl Hydroxybenzoate (0.001 to 0.1%w/v) in hot purified water in separate vessel, passing the solution through (# 60 to 100) sieve and mixing the same into the syrup of step (a), and then filtering the hot syrup bulk, preferably through a filter press, using siliceous earth as filter acid, and cooling the same to ambient temperature,

c) transferring a desired quantity (20 to 40% of syrup bulk of step (b) into another vessel,

d) dissolving polysorbate 40,60 or 80 (0.005 to 5.0%w/v) into warm purified water in a separate container and seiving the same through (# 60 to 100) sieve and adding into the syrup of step (c) under stirring to mix well,

e) transferring Azithromycin Dihydrate (4 to 5%w/v) into the mix of step (d), under continuous stirring to obtain uniform homogenous slurry free from lumps,

f) adding colloidal silicon Dioxide (0.05 to 10%w/v) to the slurry of step (e), under continuous stirring to obtain homogenous dispersion and transferring the same into the syrup bulk of step (b) kept in the manufacturing tank,

g) dissolving sodium citrate (0.05 to 5%w/v) in warm purified water in a separate vessel, sieving the solution through # 60 to 160 sieve and mixing the same into the dispersing/slurry of step (f), kept in the manufacturing tank,

h) taking hot purified water into a container, adding sodium carboxy methyl cellulose (0.1 to 0.2%w/v) under continuous stirring to form uniform slurry, sieving through # 40 sieve and mixing the same into the slurry of step (g) kept in the manufacturing tank,

i) dissolving Monoammonium Glycyrrhizinate (0.001 to 5%w/v) in warm purified water, in a separate container, under continuous stirring, filtering the solution through # 60 to 100 sieve and mixing the same into the slurry of step (h), kept into the manufacturing tank,

j) dissolving Tartrazine (0.001 to 1%w/v) in warm purified water, under continuous stirring, sieving through # 60 to 100 sieve and mixing into the slurry to step (I), kept in the manufacturing tank,

k) checking and adjusting pH, if necessary with 10% w/v sodium Hydroxide solution to maintain pH in between 7 to 9, preferably from 7.5 to 8.5,

l) homogenising the bulk preferably by passing though the colloidal mill and deaerating the product by using vacuum,

m) dissolving propylene Glycol (up to 5% w/v), Menthol (up to 5% w/v), and adding pepper mint flavour preferably C-7531 (BBA) from 0.05 to 5% w/v, in a separate vessel stirring and sieving the solution through # 60 to 100 sieve and mixing the clear solution into the bulk of step (1) kept in the manufacturing tank,

n) making up the desired volume buy mixing purified water to obtain Azithromycin oral suspension liquid composition.

2. A process as claimed in claim 1, wherein the polysorbate used in step (d) is polysorbate 60.

3. A process as claimed in claim 1 or 2 wherein the said colloidal silicon Dioxide used in step (f), is colloidal silicon Dioxide (5M).

4. A process as claimed in claim 1,2, or 3 wherein the sieving in steps (b), (d), (g), (I), (j), & (m), is carried out by using # 80 S.S. sieve.

5. A process as claimed in claim 1, wherein the said liquid composition of step (n) is subjected to sampling and analysis for approval of pH determination and Assay of Azithromycin.

6. A process as claimed in claim 1,2,3,4 or 5 wherein the said liquid composition after approval of pH determination and Assay of Azithromycin is filled in suitable containers preferably amber glass bottles under continuous moderate stirring and sealed, preferably with pilfer proof aluminium cap with E.P. Wad.

7. A process as claimed in any of the preceding claims wherein the said manufacturing tank is a steam jacketed stainless steel (S.S.) manufacturing tank.

8. A process as claimed in any of the preceding claims wherein the said other vessels and/or containers used are made of stainless steel.

9. A process as claimed in any of the preceding claims wherein the said vessels and/or containers are rinsed with purified water and rinsing is added and mixed to the bulk in the manufacturing tank.

10. A process of preparing Azithromycin oral suspension liquid composition, substantially as herein described and illustrated in the examples.

Dated this 24th day of May, 2000.

V. ANURADHA RAMU

Agent for the Applicant.

FORM - 3

THE PATENTS ACT, 1970

PROVISIONAL
SPECIFICATION

SECTION 10

TITLE : **A PROCESS OF PREPARING STABLE AZITHROMYCIN ORAL SUSPENSION LIQUID COMPOSITION**

APPLICANT : **M/s.ALEMBIC CHEMICAL WORKS COMPANY LIMITED, ALEMBIC ROAD, VADODARA 390 003, GUJARAT. AN INDIAN COMPANY INCORPORATED UNDER THE COMPANIES ACT,1956**

The following Specification describes the nature of this invention:-

This invention relates to manufacturing AZITHROMYCIN ORAL SUSPENSION LIQUID

The Present Composition of AZITHROMYCIN ORAL SUSPENSION LIQUID is as follows:

Azithromycin Dihydrate

Sucrose

Sodium Methyl Hydroxy Benzoate

Sodium Propyl Hydroxy Benzoate

Xanthan Gum

Colloidal Silicon Dioxide (5M)

Polysorbate 60

Sodium Citrate

Propylene Glycol

Menthol

Monoammonium Glycyrrhizinate

Tartrazine

Peppermint Flavour C-7531 (BBA)

Purified Water

The Present Process for msnufacturing AZITHROMYCIN ORAL SUSPENSION LIQUID is as follows:

1. Transfer Purified Water to a steam jacketted s.s. manufacturing tank. Add sucrose and heat till it is completely dissolved.
2. Filter the syrup through Hyflow into another suitable manufacturing tank and cool the syrup.
3. Transfer part of the syrup to a suitable s.s.vessel.

4. Dissolve Polysorbate 60 in Purified Water and add to the above vessel.
5. Transfer Azithromycin Dihydrate to the above vessel with continuous stirring.
6. Disperse Xanthan Gum in Purified Water and transfer to the above vessel.
7. Transfer Colloidal Silicon Dioxide to the vessel with continuous stirring.
8. Dissolve Sodium Methyl Hydroxy Benzoate and Sodium Propyl Hydroxy Benzoate in Purified Water and add to the manufacturing tank.(Step 2)
9. Transfer the contents of Step 7 to the manufacturing tank with continuous stirring.
10. Dissolve Sodium Citrate in Purified Water and add to the manufacturing tank.
11. Dissolve Monoammonium Glycyrrizinate in Purified Water and add to the manufacturing tank.
12. Dissolve Tartrazine in Purified Water and add to the manufacturing tank.
13. Pass the suspension through the colloidal mill and dearate the product under vacuum.
14. Check and adjust the pH to 8.2, if necessary with 10% solution of Sodium Citrate.
15. Dissolve Menthol in Propylene Glycol and transfer to the manufacturing tank.
16. Transfer Peppermint Flavour to the manufacturing tank.
17. Make up the volume with Purified Water and mix.

The Improved Composition in accordance with this invention is as follows:

Azithromycin Sucrose

Sodium Methyl Hydroxy Benzoate

Sodium Propyl Hydroxy Benzoate

Sodium Carboxymethyl Cellulose

Colloidal Silicon Dioxide (5M)

Polysorbate 60

Sodium Citrate

Propylene Glycol

Glycerol

Menthol

Monoammonium Glycyrrhizinate

Tartrazine

Peppermint Flavour C-7531 (BBA)

Purified Water

The Improved Process in accordance with this invention is as follows:

1. Transfer Purified Water to a steam jacketted s.s. manufacturing tank. Add sucrose and heat till it is completely dissolved.
2. Filter the syrup through Hyflow into another suitable manufacturing tank and cool the syrup.
3. Transfer part of the syrup to a suitable s.s.vessel.
4. Disperse Azithromycin Dihydrate and Colloidal Silicon Dioxide in Polysorbate 60 to get a uniform slurry and add to the above vessel.
5. Disperse Sodium Carboxy Methyl Cellulose in Purified.

7. Dissolve Sodium Methyl Hydroxy Benzoate and Sodium Propyl Hydroxy Benzoate in Purified Water and add to the manufacturing tank.(Step 2)
8. Transfer the contents of Step 7 to the manufacturing tank with continuous stirring.
9. Dissolve Sodium Citrate in Purified Water and add to the manufacturing tank.
10. Dissolve Monoammonium Glycyrrizinate in Purified Water and add to the manufacturing tank.
11. Dissolve Tartrazine in Purified Water and add to the manufacturing tank.
12. Pass the suspension through the colloidal mill and dearate the product under vacuum.
13. Check and adjust the pH to 8.2, if necessary with 10% solution of Sodium Citrate
14. Dissolve Menthol in Propylene Glycol and transfer to the manufacturing tank.
15. Transfer Peppermint Flavour to the manufacturing tank.
16. Make up the volume with Purified Water and mix.

Advantages of Improved Composition/Process

Sodium Carboxy Methyl Cellulose is more stable in alkaline solutions and exhibits a greater viscosity and stability at the pH of the product i.e.7 - 9. Being a synthetic polymer, it is available in highly purified form and batch to batch variation is very less.

The use of Polysorbate 60 with Azithromycin Dihydrate and Colloidal Silicon Dioxide provides a uniform and stable suspension.

The addition of Glycerol improves the taste and preservation efficacy of the product. It also imparts Viscosity to the product.

Raw materials for Azithromycin Liquid

Active Ingredient	% w/v
Azithromycin Dihydrate USP	4.200
Pharmaceutical Aids	
Sweetening Agent	
Sucrose	75.00
Preservatives	
Sodium Methyl Hydroxy Benzoate	0.100
Sodium Propyl Hydroxy Benzoate	0.050
Viscosity Imparting Agent	
Xanthan Gum	0.100
Wetting Agent	
Polysorbate 60	0.100
Artifical Sweetening Agent	
Monoammonium Glycyrrhizinate	0.800
Colouring Agent	
Tartrazine	0.020

Flavouring Agent	
Menthol	0.005
Peppermint Flavour	0.400
Vehicl	
Purified Water	q.s.

Experimental Trials made during Development of Azithral Liquid.

Preservatives	
Sodium Methyl Hydroxy Benzoate	0.100% w/v
Sodium Propyl Hydroxy Benzoate	0.050% w/v
Sodium Benzoate	0.100 and 0.200% w/v

Use of Sodium Benzoate imparts bitterness to the product.

Viscosity Imparting Agents

Sodium Carboxy Methyl Cellulose	0.200,0.300 and 0.400%w/v
Hydroxy Propyl Methyl Cellulose	0.200 and 0.300% w/v
Xanthan Gum	0.075,0.100 and 0.125%w/v

Use of Sodium Carboxy Methyl Cellulose gives better suspension quality as compared to Hydroxy Propyl Methyl

viscosity to the product. At a concentration of 0.100% w/v, a satisfactory product is obtained.

Suspending Agent

Colloidal Silicon Dioxide (5M)	0.200, 0.300 and 0.400%w/v

Concentration of 0.200% w/v was found to impart creaming of the Active Ingredient while 0.400% w/v leads to the caking of the product.

Wetting Agents

Polysorbate 60	0.050, 0.100 and 0.150% w/v
Polysorbate 80	0.050 and 0.100% w/v

Use of polysorbate 80 imparts an unpleasant taste to the product even at the concentration of 0.05% w/v.

Use of polysorbate 60 does not impart any unpleasant taste to the product.

Concentration of 0.05% w/v of Polysorbate 60 gives poor suspension quality while 0.15% w/v leads to the caking of the product.

Buffering Agents

Sodium Citrate	pH 8.5 and 10.0
Dipotassium Hydrogen Phosphate	pH 8.5 and 10.0
disodium Hydrogen Phosphate	pH 8.5 and 10.0

Use of Sodium Citrate gives better taste at pH 8.5 as compared to pH 10.0

Flavouring Agents

Different flavours without and with different concentrations of menthol were tried.

Following flavours were tried.

	With Menthol	Without Menthol
Mango flavour	5.00 mg%	0.100% v/v
Mixed Fruit flavour	5.00 mg%	0.200% v/v
Peppermint flavour	5.00, 12.5 and 25.0 mg%	0.300 and 0.400% v/v

Peppermint flavour with higher concentration of 0.400% v/v with 5.00 mg% menthol gives good palatability, taste initially and also on shelf life.

Co-solvents

Propylene Glycol

Polyethylene Glycol 400

Use of Polyethylene Glycol 400 imparts unpleasant taste to the product.

Artifical Sweetening Agents

Sodium Saccharin	0.200 and 0.300% w/v
Aspartame	0.500 and 0.700% w/v

Use of Sodium Saccharin gives good palatibility to the product. However, it is not recommended for paediatric preparations.

Aspartame was found to give an unpleasant taste in the product on agening, due to its poor stability in alkaline medium.

Monoammonium Glycyrrhizinate at the concentration of 0.80% w/v was found to give better taste to the product on ageing.

Colouring Agents

Tartrazine	20 mg%
Sunset Yellow	10 mg%
Quinoline Yellow	20 mg%

Sunset Yellow colour fades on accelerated stability studies.

Colour shade with Tartrazine is better in appearance compared to Quinoline Yellow.

Dated this 23rd day of February 1999

V. RAMU
of RAMU & ASSOCIATES
Applicants' Patent Attorney